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Long-term European Strategies in Predictive, Preventive and Personalised Medicine

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Abstract. *Current healthcare practices essentially rely on emergence of signs and symptoms of human pathologies prior to initiation of interventional modalities. A major limitation of this approach relates to the fact that often the disease process has already taken its toll through manifestation of its complications. As a result, despite high costs associated with care of these individuals, long-term prognosis usually remains poor due to inadequate control of disease manifestations, treatment failure, disease-recurrence and the appearance of severe secondary complications, among others, thereby contributing to relatively poor life-quality of the treated persons, high morbidity and mortality. Personalised medicine is a new philosophy in the healthcare aimed at a potential application of innovative bio-technologies in the prediction of human pathologies, a development of well-timed prevention and individualised therapy-planning. These coordinated measures should be well-focused on solving the accumulating problems in the European healthcare and worldwide. The mission of the European Coordinator in this field is performed by the "European Association for Predictive, Preventive and Personalised Medicine" (EPMA; www.epmanet.eu).*

Predictive medicine is an attractive subject for research activities aimed at the prediction of human pathologies, a development of well-timed prevention and individual therapy-planning. The issue has several aspects which allow the expectation of great advantages for predictive diagnosis and personalised treatment as the medicine of the future. Amongst the most important of these aspects are well-organised population screening, the targeted prevention of frequent pathologies, non- or minimally invasive diagnostic procedures, optimal therapy planning, personalised patient treatment, substantial improvement of the quality of life and plausible solutions for particular social and ethical as well as serious economic problems. Such decisive progress can be achieved only by the well-coordinated fulfilment of the following components that are crucial for the practical realisation of this new philosophy in healthcare: adequate investment creating novel technologies; development of non- or minimally invasive diagnostic tools; a well-organised process for the exchange and transfer of knowledge between biomedical research entities and biotechnological industries for production of advanced diagnostic tools; quality assurance through the introduction of international standards for technological tools and devices, patenting and licenses; correct professional education in terms of the application of biotechnological high-tech procedures in medicine; intelligent political regulations in the healthcare sector including introduction of obligatory guidelines and clear regulations for the health insurance industry to ensure that patients needs are met; measures to ensure confidentiality of patient information and personal databank and distribution of relevant information among healthcare professionals and users.

These coordinated measures should be well-focused on solving the accumulating problems in healthcare and the concomitant economic burden that societies across the globe are facing more and more. The mission of the European Coordinator in this field is performed by the "European Association for Predictive, Preventive and Personalised Medicine" with the following objectives registered in Brussels by the "Statutes" of the Association: Raising awareness and recognition of Predictive, Preventive and Personalised Medicine (PPPM) throughout all Member Countries of the European Union and Associated Countries; Providing and disseminating accurate and up-to-date information and educational materials on Predictive and Personalised Medicine and targeted preventive measures; Encouraging the adequate allocation of resources for PPPM; Encouraging and suggesting advanced programmes for personalised patient treatment; Promoting high-quality research focused on predictive diagnosis and personalised patient treatment; Promoting the standardisation of bio-

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analytical technologies for predictive pre-clinical and clinical applications; Consolidating professionals for an effective European Network in PPPM; Coordinating multidisciplinary efforts in PPPM; Having an advisory role in issue-related international / national projects as the official European Representative of PPPM; Contributing to the creation of Guidelines in European healthcare with the accentuated role of prediction, prevention and personalised patient treatment in favour of improved life-quality of the European population.

The Association is clearly structured in order to reach the best possible coordination of the PPPM-related multifaceted activities over Europe: there are National Representatives in all 27 Member Countries of the European Union and the Associated Countries (*e.g.* Israel, Serbia, *etc.*). The group of National Representatives is the key-element in the structure of the Association which consolidates and coordinates the EPMA (European Association for Predictive, Preventive and Personalised Medicine)-related activities at the national level closely working with all PPPM-related national institutions, units and groups such as Federations of Patients, Universities, research units, state and private hospitals, industrial groups, political representatives, insurance, etc. The group of National Representatives considers the problems which EPMA poses in the realisation of its objectives in individual national healthcare systems.

The solutions for the reported PPPM-related problems as well as consolidated ideas for innovative European and international projects, which the EPMA represents for their consideration at the EU-Commission and the European Parliament, are worked out by a consortium of world-leading professionals (Europe-unrestricted) divided between two closely cooperating "Advisory Boards" of EPMA – the Academic and Industrial. The number of members is limited to fifteen in each of these and professionals are strictly selected for membership of the Board according to the highest worldwide well-acknowledged issue-related qualifications. As a result of these consolidated efforts, crucial progress is expected for more innovation and reliability in PPP-related research activities and scientific publications; highly active transfer of knowledge between academia and industry and realistic application of PPPM-related approaches in European healthcare.

The central organisation of the EPMA is led by the "Board of Directors" which is constant for the Association and consists of Vincenzo Costigliola (Brussels, Belgium) – The President; Olga Golubnitschaja (Brussels, Belgium / University of Bonn, Germany) – The Secretary-General; Silvia Mandel ("Technion", Haifa, Israel) – Vice-President responsible for the Associated Countries and contacts apart from Europe; Kurt Krapfenbauer (University of Vienna, Austria) – Vice-President responsible for European Affairs; Marko Kapalla (Negentropic Systems, Slovakia) – Director responsible for contacts with industry; Peter Gahan (King's College, London, UK) – Director responsible for the education; Heinz Lemke (University of Leipzig, Germany) – Director responsible for the innovative technologies; John G. Delinassios (International Institute of Anticancer Research, Athens, Greece) – Director responsible for publicity.

All the EPMA-activities are summarised on the website www.epmanet.eu. As can be seen there, the patients are the focus of the EPMA, since the real application of innovative technologies for predictive diagnosis, targeted preventive measures and personalised patient treatment in European healthcare is the central premise of the Association.

The initial discussions for the establishment of EPMA-Network took place at the 1st Workshop on the Predictive, Preventive and Personalised Medicine, 13th-14th November 2008, Brussels, Belgium. The abstracts of the Workshop, printed here, justify the necessity for the creation and support of EPMA.

Abstracts

1
ZINC FINGER NUCLEASE-MEDIATED GENE REPAIR AS A GENERIC APPROACH TO INDIVIDUALISED MEDICINE

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Our knowledge of how mutations cause disease dramatically outstrips our ability to treat the consequences of their effects. An obvious solution, gene repair, has never featured as a realistic clinical approach to date, as existing protocols typically repair just one cell in a million. In 2005, the use of a new class of synthetic enzymes known as zinc finger nucleases (ZFNs), led to a seismic improvement in gene repair efficiency with the correction of as many as 20% of treated cells within 72 hours. Moreover, the gene repair is permanent, and can be targeted to any gene in the genome simply by manipulating the DNA binding specificity of the ZFNs. Subsequent studies have shown that the ZFN gene repair system can be delivered using virus vectors, and ZFN-modified cells have been successfully transferred back into animals. This technology seems to offer a route to the ultimate goal of individualised medicine; if a gene defect is known, then ZFNs can be created to target and repair it. Indeed, where efficient gene delivery protocols already exist, the immediate question is which genes should be targeted for ZFN-mediated repair. A thorough evaluation of this new technology is needed before talking of a clinical revolution.

2
CIRCULATING NUCLEIC ACIDS IN PLASMA AND SERUM (CNAPS) IN PREDICTIVE MEDICINE

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Low levels of DNA and RNA are constantly present in circulating blood plasma (1.8-3.5 ng DNA and about 2.5 ng RNA per ml blood). Increases in these DNA/RNA blood levels (sometimes to as high as 3,000 ng per ml) occur during a number of pathological disorders. Hence the increases in the levels of specific DNA and RNA have allowed the early identification of a range of disorders including trauma, stroke, myocardial infarct, cancer (*e.g.* lung, colorectal, liver, prostate, breast and oesophageal carcinomas), diabetes, transplant rejection, pre-eclampsia and foetal disorders (*e.g.* rhesus factors, achondroplasia, β-thalassaemia, trisomy 13 and 21). The specific marker DNA or m-RNA is identified by nucleic acid isolation from peripheral blood and augmentation by real-time-PCR or RT-PCR prior to either gel electrophoresis or mass spectrometry. Monitoring of treatment may also be achieved with successful treatment resulting in the return to normal of the DNA levels. Accurate prognosis has also been predicted for some malignancies, trauma and stroke.

The origin of the increased DNA is primarily from either apoptosis of *e.g.* tumour cells or the spontaneous release of newly synthesised DNA. RNA may also be released by apoptosis although the spontaneously released DNA has associated RNA.

3
ACTIVE RELEASE OF NUCLEIC ACIDS BY LIVING CELLS OF HIGHER ORGANISMS GOVERNED BY A HOMEOSTATIC MECHANISM

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In higher organisms, DNA is permanently released from living cells in a nucleoprotein complex with lipids. This is not related to dead or dying cells and takes place within an active homeostatic system. The high specific activity of the released DNA suggests a preferential release of newly synthesised DNA. The released complex contains also RNA and enzymes such as a DNA-dependent DNA polymerase and an RNA-dependent DNA polymerase. When a phosphorylated-precusor is added to a cell free supernatant, the DNA recovered from the medium is labelled. Nearest neighbour analysis of the labelled DNA shows true precursor incorporation.

Circulating tumour-specific nucleic acids have been identified in plasma and serum. This has opened a new field of research in cancer detection within a non-invasive blood test. Similarly, the discovery of cell-free fetal nucleic acids in maternal plasma allows non-invasive prenatal diagnosis.

Additionally the released complex has a high power of transformation, which might open up better gene treatment possibilities.

4
PREDICTIVE DIAGNOSIS OF LIFE-LONG CHRONIC PATHOLOGIES IN ASPHYXIATED NEWBORNS

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The leading perinatal complication is birth asphyxia – insufficient oxygen supply that can cause severe hypoxic ischemic organ damage in newborns followed by either a fatal outcome or severe life-long pathologies. Increased morbidity and mortality, hypoxic-ischemic encephalopathy, mental retardation, neurodegenerative diseases, nephropathy, cardiomyopathy, vascular pathologies, senescence, *Diabetes mellitus* and cancer all belong to the short- and long-term outcomes of birth asphyxia.

The diagnostic approaches based on pathology-specific molecules are promising in predicting an individual predisposition to particular disorders and so serve as the selective targets for preventive therapeutic measures. Thus, our recent results show significant expression activation of TAU-protein in the blood of experimental rats after the onset of severe asphyxic insult. An increase in TAU-levels is characteristic of Alzheimer's disease and has been implicated in the molecular mechanisms of its pathology. TAU-protein should be considered as a pathology-specific biomarker, useful as a predictive blood test for asphyxiated newborns.

5
PREDICTIVE AND PREVENTIVE DIAGNOSIS IN REPRODUCTIVE MEDICINE

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Reproductive medicine includes issues relevant to the physiology of reproduction and to fetal and embryonic health, such as infertility, recurrent pregnancy loss, foetal abnormalities, pre-eclampsia, preterm labor, intrauterine growth restriction (IUGR), maternal health etc. Prediction and the prevention of the pathological situations of human reproduction and foetus health, demand the use of rapid, non-invasive, accurate, high-throughput and cost effective methods. Proteomics has all the necessary attributes to identify biomarkers, while mass spectrometry (MS) offers rapid and sensitive methods which could be applied in prediction and prevention issues. Although proteomic technology in reproductive medicine is still in its infancy, characterisation of the reproductive tissue and fluids proteome and identification of disease biomarkers can be expected to significantly improve maternal and embryo healthcare. The use of MS represents a new opportunity that can potentially allow early diagnosis of fetal abnormalities and pregnancy complications, and in the future could facilitate the development of effective therapeutic interventions. In order to tackle these complications we propose a cutting edge approach combining proteomics, peptidomics, MS and bioinformatics. That approach will institute the potential of protein-oriented non-invasive prenatal diagnosis of fetal abnormalities and pregnancy complications and uncover the molecular mechanisms implicated in these conditions leading to new therapeutic interventions.

6
BIOMARKERS FOR PREDICTION AND TARGETED PREVENTION OF ALZHEIMER'S DISEASE

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During the last century the world population has shown a staggering increase in its proportion of elderly members. All epidemiological studies of Alzheimer's dementia show a strong correlation between prevalence and age. The prevalence of dementia doubles approximately every 5 years after the age of 65 reaching about 50% among those aged 90 years or older. The pathological process characteristic of Alzheimer's disease (AD) begins years before the first symptoms of brain failure, thus making it difficult to reliably identify pathology based on the clinical phenotype alone. Therefore, the availability of biological markers (BM) for early disease diagnosis would impact the management of AD by identifying high-risk individuals before symptoms develop and helping to discriminate between true AD and other neurodegenerative processes or demented individuals. Of particular importance, BM would enable the clinical efficacy of new neuroprotective therapies to be determined. The optimal approach would be the implementation of combined biomarkers including the standard genetic, neuroimaging and biochemical together with novel peripheral blood BMs. A combination of circulating lymphocyte mRNA profiling and serum proteome would provide novel molecular signatures for the prediction of "at risk" individuals or for early detection and treatment follow-up.

7
PREDICTION IN BREAST CANCER

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Why early and predictive diagnosis is crucial for long-term outcomes of breast cancer. Breast cancer is the most common cause of cancer death among women with an average incidence rate of 10-12 per 100 women. In 2005, breast cancer led to 502,000 deaths worldwide. Advanced stages of breast cancer lead to the development of metastasis predominantly in the lymph nodes, bone, lung, skin, brain, and liver. Although breast-MRI is currently the most sensitive diagnostic tool for breast imaging, its specificity is limited resulting in a negative impact for surgical management in approximately 9 % of cases. Early diagnosis has been demonstrated to be highly beneficial, enabling significantly enhanced therapy efficiency and possibly full recovery.
Non-invasive approaches in breast cancer prediction. In addition to the increased risk of tumour-spreading by invasive biopsies, a serious disadvantage of utilising biopsy samples for molecular imaging is the mixed cell population obtained, strongly varying from case to case, and resulting in differential gene expression with limited specificity related to the pathology. A central concept of non-invasive diagnosis focuses on blood-tests for the prediction of an individual's predisposition. Pathology-specific expression patterns have been demonstrated in circulating leukocytes that make blood tests of realistic use in the predictive diagnosis of breast cancer.

8
PERSONALISED PATIENT TREATMENT IN BREAST CANCER: PROGNOSIS OF INDIVIDUAL TREATMENT TOXICITY

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Breast-conserving lumpectomy followed by radiation therapy has been shown to be an alternative strategy, competitive to mastectomy, in preventing mortality caused by breast cancer. However, besides negative short-term effects (blood flow disturbances, painful erythema, *etc*.) breast irradiation causes severe long-term side-effects (leucopenia, anemia, breast edema, fibrosis, increase of angiosarcoma, leukemia, myelodysplastic syndromes). Therefore, the identification of individual susceptibility to radiation and improved patient-specific radiotherapy planning are highly desirable for personalised treatment in breast cancer.

Some recently developed, advanced diagnostic approaches focus on minimally invasive blood analysis as a valuable source of information concerning individual stress reactions under irradiation treatment. The prognostic role of leukocyte activity in breast cancer patients has long been recognised. Although fluctuating considerably among both node-negative and -positive patients, this activity has been demonstrated to be significantly lower in patients with a greater tumour burden. The authors emphasise the necessity for a more comprehensive analysis that would consider late effects of radiotherapy, stress-response and repair kinetics in terms of diagnostic and prognostic purposes in favour of the personalised treatment of breast cancer patients.

9
EDUCATIONAL MEASURES AS PREVENTION OF BIRTH ASPHYXIA

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Birth asphyxia is a global health problem leading to some million newborn deaths annually. Both mild and severe stress by birth asphyxia can trigger several neurodegenerative, cardiovascular, cancer and other pathologies which often appear in childhood and adulthood.

Recent population studies have stressed the importance of the educational level in preventing birth asphycia. The professional status and educational level of the parents has been demonstrated to be crucial for a physiological (normoxia) birth. Moreover, significant differences in the incidence rate of birth asphyxia exist among professional groups with the highest frequency of birth asphyxia tending to be in uneducated, unemployed parents. Thus, the educational factor is considered to be crucial in the prevention of birth asphyxia worldwide. Therefore, proper educational programmes can have a highly-positive impact on the prevention of the most severe perinatal complications and overall perinatal morbidity.

10
NOVEL IMAGING TECHNOLOGIES IN EARLY GLAUCOMA DIAGNOSIS

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Essential role of prediction and prevention in glaucoma. Glaucoma is a neurodegenerative eye disease and the second leading cause of permanent vision loss with an estimated 67 million patients worldwide. The molecular pathomechanisms of glaucoma demonstrate both a considerable overlap with and remarkable particularities compared to some other neurodegenerative disorders *e.g.* Alzheimer's disease. Therefore, the selection of a set of key molecules, the expression levels of which are specifically affected by glaucoma, would be particularly valuable for the development of highly precise molecular diagnostic approaches.

Impact and imaging of vascular deregulation in glaucoma pathology. A wealth of literature points to the importance of haemodynamics in glaucoma pathology. Vasospasm defined as an inappropriate constriction or insufficient dilatation in the microcirculation is frequently observed in glaucoma patients.

Imaging of DNA-damage and repair capacity in vasospasm and glaucoma. In glaucoma, comparative "Comet Assay" analysis demonstrates significantly enhanced DNA damage compared to both healthy vasospastic and non-vasospastic individuals and reveals pathology-specific comet patterns.

Altered gene expression patterns in blood as the basis for the development of novel molecular imaging technologies in early glaucoma diagnosis. The following key pathways are affected in glaucoma pathology: stress response, apoptosis and DNA-repair, adhesion, blood-brain-barrier-breakdown, tissue remodelling, transcription regulation, multi-drug resistance and energy metabolism.

11
PROGNOSIS AND INDIVIDUALISED THERAPY IN GLIOMA TREATMENT

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Malignant gliomas are highly lethal cancer diseases. The diffuse character of the tumour periphery makes post-operative treatment of gliomas particularly complicated. Thus, median survival of 14.6 and 12.1 months was demonstrated when either chemoradiation or radiation alone had been applied. Irrespective of the treatment, glioblastoma patients have been shown to benefit from epigenetic silencing of MGMT (O6-methylguanine-DNA-methyltransferase) expression, DNA-repair activity of which was compromised by promoter methylation (an independent favourable prognostic factor associated with longer survival in patients with glioblastoma). The fact that those patients whose tumours are not methylated at the MGMT-promoter do not benefit from temozolomide (TMZ) treatment, suggests a predictive role of MGMT methylation status in therapy response towards TMZ-treatment. For these patients, alternative treatment approaches should be applied. However, under TMZ-treatment significant differences in survival (range of 17 to 30 months) have been demonstrated even for patients whose tumours were methylated at the MGMT-promoter. Depending on the patient, individual data measured in the primary human glioblastoma cells showed a wide range of response to TMZ treatment *in vitro*. This finding calls for further predictors of individual therapeutic responses in treated glioblastomas. Therefore, molecular mechanisms of therapy resistance are of particular interest in malignant glioblastomas with a hypermethylated MGMT-promoter.

12
PREDICTIVE FACTORS IN HEAD AND NECK CANCER MANAGEMENT

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A great variety of protocols including surgical, radiotherapy and chemotherapy approaches alone or combined have been designed in the past in order to achieve the best results for the treatment of head and neck cancer. Also, there are several reports in the literature related to various predictive factors and their influence on the final outcome of the treatment. Head and neck cancer is known to be a multifactorial disease. Our studies correlating genetic factors with individual susceptibility and tobacco smoking with clinical and bio-pathological data in our patient population are presented. We believe that in the future we should look more carefully at those factors that may influence the decision for the most appropriate protocol strategy prior to the beginning of treatment, predict the results of its treatment and monitor the final outcome. Although we recognise that this new area of

genetic onco-biology is not familiar to most otolaryngologists, we want to call their attention to it and to spread information regarding its role in the current management of this disease.

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PREDICTIVE DIAGNOSIS AND PERSONALISED TREATMENT OF CANCER IN *DIABETES MELLITUS*

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Diabetes mellitus (DM) is a group of metabolic disorders, mainly characterised by impaired glucose metabolism and hyperglycemia as common features. There is a growing body of evidence that DM predisposes to almost all cancer types with some particular susceptibilities. Although the pathomechanisms of cancer in diabetes are currently largely unclear, some particularities in molecular pathways that can predispose diabetics to cancer have been identified. Thus, disturbed glucose/insulin homeostasis increases the production of reactive oxygen species and oxidative damage to chromosomal and mitochondrial DNA is frequently observed in diabetics. Long-term accumulation of DNA mutations is well-acknowledged as triggering cancer. Mitochondrial dysfunction might be implicated as a pathomechanism of diabetes-provoked cancer. In addition, diabetic patients are a high-risk group for infectious disorders including viral infections. In turn, viral infections are implicated in cancer pathology. Recent studies have demonstrated significant alterations in the protein profiles of cancer-bearing diabetics compared to cancer patients without a diabetic history, that should be taken into consideration when developing pathology-specific diagnostic approaches. Pathology specific marker-candidate profiling in blood samples might be potentially useful for the development of non-invasive predictive and diagnostic tools that could be applied in diabetic care for targeted preventive measures and individualised therapeutic strategies.

14
PREDICTION AND TARGETED PREVENTIVE MEASURES IN DIABETES CARE

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The essential role of predictive, preventive and personalised medicine in diabetes care. The ever increasing number of diabetic patients presents a serious health-care challenge to most industrialised countries and developing societies with large populations: every 10 seconds one patient dies of diabetes-related consequences. Given the high risk and prevalence of secondary complications as well as individual predisposition to target organ injury, diabetic pathology is one of the best examples for the application of predictive diagnosis aimed at preventive measures and personalised treatment approaches.

Proposed solutions - creation and application of innovative technologies. Prevention of diabetes and its complications represents a major challenge for societies on a global scale. This task requires well-coordinated multifaceted approach which should be performed in concert using broad multidisciplinary expertise. A consistent program of targeted measures should be developed. The following components (a-f) and advanced technologies should be further considered for the practical realisation of the programme for the prevention of DM: a) education and b) individualised nutrition; as predictive diagnostic tools: c) novel molecular targets and d) non-invasive diagnostic approaches; e) targeted prevention of severe complications secondary to diabetes and f) personalised treatment of diabetics.

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MEDICAL PRACTICE IN DIABETES CARE

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Diabetes mellitus is a serious medical problem that causes long-term systemic complications and considerable associated morbidity. In 2007, there were an estimated 246 million people with diabetes, predicted to rise to 380 million by 2025. Overall costs of care range from 2.5% to 15% of annual health budgets. Diabetes is the most common cause of blindness in people of working age. In the USA 3.6% of patients with type 1 and 1.6% of patients with type 2 diabetes are legally blind. In England and Wales, 1,000 patients with diabetes are registered blind or partially sighted every year.

The current treatment strategies such as laser photo-coagulation, pars plana vitrectomy and anti-angiogenic drugs do not always give satisfactory results in the treatment or the prevention of complications of diabetic maculopathy and retinopathy.

The latest advances promote a need for an “interdisciplinary mind” and an understanding of the molecular basis of the therapeutic strategies. The goals of predictive medicine are to

provide a future investigative direction and by dissipating knowledge of the pathophysiological mechanisms, to lead consequently to individualised therapeutic approaches.

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CONVENTIONAL AND EMERGING TREATMENTS IN *DIABETES MELLITUS*: IMPROVED DRUG-DELIVERY SYSTEMS

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Novel diabetes treatment approaches are expected to enhance their quality and efficiency during the coming years. As for the last years, several advanced technologies have been developed resulting from an enormous effort to solve the problems in diabetes care. Advanced controlled delivery systems present indubitable advantages for pharmacologically active compounds administration. The generic aim of diabetes therapy is coupling the sensing of blood glucose to the rapid release of the right amount of insulin. This mechanism enables to maintain normal glucose levels, independently of dietary intake and improve the clinical status of diabetics. Due to the epidemic scale of *Diabetes mellitus*, novel drug delivery systems play an important role in and are highly relevant to improve the treatment of worldwide permanently growing subpopulation of diabetic patients. The research efforts are expected to bring new insights into the regulatory mechanisms involved in both diabetes type 1 and 2 that can potentially lead to the conditions close to the physiological ones in terms of insulin secretion in response to the altering blood glucose levels. For the same purposes, the improved synthetic methods to prepare/modify novel drug-delivery systems (*e.g.* polymers) are of prime importance for the targeted organ-specific patient treatment.

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PATIENT VIEW

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The current percentage of diabetics is already very high in Germany and worldwide; moreover, these numbers are increasing dramatically. It is absolutely clear that diabetes is a severe pathology which should be considered very seriously. Unfortunately the current diabetes care is far from being good enough: there is a very long list of patients, who were diagnosed by chance and too late. Currently, diabetics are treated "across-the-board", although it is becoming absolutely clear that personalised treatment is life-important for diabetics. This unsatisfactory situation should be dramatically changed in the near future through the current technological progress in predictive and personalised medicine.

18
THE EU 7TH FRAMEWORK PROGRAMME AND ACTIVITIES FOR PREDICTIVE MEDICINE

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A short overview of what predictive medicine could do, with a few already existing examples is presented. This is followed by a description of the European Union's 7th Framework Programme for research and technological development (FP7), its budget, its structure and detailing the Health research aspects more fully, with the example of the "Detection, Diagnosis and Monitoring" area (DDM). Some statistics of the projects supported up to now in the FP7 are given with the examples of those in the DDM area concerning both *in vitro* molecular testing and *in vitro*/*in vivo* biomedical imaging. Topics open for the next, third call for proposals, and potential publication of the fourth call (tentative period: end July 2009), are invited.

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PHARMACOGENETICS AND PREDICTION OF DRUG RESPONSE

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The personalised medicine model in the pharmaceutical industry reflects one viable solution to the well published fact that marketed drugs often achieve partial or suboptimal response rates in clinical practice. The underlying causes and modifiers of drug response are numerous, with the factors contributing the largest effects being environmental (*e.g.* diet and co-medication) and avoidable medication errors, as well as heritable genetic predisposition (25-50%) un-expressed in the course of an individual's life unless challenged by a particular drug stimulus. Pharmacogenetics (PGX) is the study of DNA sequence variation as related to drug response (efficacy, safety and dosing). Since constitutional germ-line

polymorphisms are stable throughout an individual's life, they can serve as predictive markers facilitating the optimization of early stage clinical interventions prior to the manifestation of detrimental symptoms. Therefore, PGX is considered one of the basic constituents of the personalised medicine tool-kit and is becoming integral to the drug development process.

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MODEL-BASED PATIENT CARE WITH A THERAPY IMAGING AND MODEL MANAGEMENT SYSTEM

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In the day-to-day practice of medicine, most of the diagnostic and therapeutic activities are performed with incomplete knowledge, or with varying levels of certainty. Bayesian systems, here represented by means of a patient-specific model based on multi-entity Bayesian networks (MEBN), provide well-established, statistically-based methods of dealing with conditions in which there is incomplete knowledge or varying levels of certainty. MEBNs can contribute to the organisation and understanding of medical knowledge associated with the patient-specific model of a therapy imaging and model management system (TIMMS).

Modern IT architectures and a dramatic increase in available computer processing power and communication bandwidth allow new healthcare services enabling personalised medicine. Model guided therapy (MGT) and the patient specific model (PSM) are the keys to realizing this personalised medicine.

Using the MEBN method and through the appropriate and comprehensive collection and processing of patient-specific data before, during and after a medical therapeutic intervention, enough patient-specific knowledge can be made available and added to the PSM. This knowledge can then be utilised to achieve substantial improvement in predicting the effectiveness and in performing patient-specific MGT, and thereby providing the basis for personalised medicine.

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RESULT INTERPRETATION IN LABORATORY DIAGNOSIS MAY SUPPORT THE POTENTIAL OF PREDICTIVE, PREVENTIVE AND PERSONALISED MEDICINE

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Patient sample processing conventionally recognises three phases: pre-analytical, analytical and post-analytical. While the first two are well recognised and great attention is paid to their quality improvement, the post-analytical phase now emerges as crucial if it is to support the entire concept of prediction and prevention.

Results acquired in the analytical process should be interpreted not only in the context of the commonly used reference values, but attention should be focused on the analysis of results in comparison with the previous results of the particular patient and particular test. Taking into consideration the biological variation and analytical performance of the laboratory, simple statistical methods may be used to determine if the result significantly differs from the previous one even if both results lie within the reference range. Since two results can differ significantly from a statistical point of view, yet clinically the difference may be irrelevant, it is important to analyse a sequence of several results in order to give a plausible interpretation of possible trends or patterns in the results. Achieving such progress in result interpretation requires changes in laboratory information systems, high level of analytical performance, reliable clinical data and education of the physicians on this topic.

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BIOMARKERS FOR PREDICTION AND PREVENTION OF PARKINSON'S DISEASE

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To date the diagnosis of Parkinson's disease (PD) is based on symptom's evaluation and on neuroimaging analysis. No tests based on biochemical markers in blood or cerebrospinal fluid are as yet available, whereas tests for early predictive symptoms are just beginning to be recognised. Potential early predictive symptoms could be summarised as: sleep disturbance, depressed mood, mild cognitive impairment and olfactory deficits together with autonomic dysfunctions. Biochemical tests could be summarised as: abnormalities in dopamine signalling and mitochondrial functions; variations in prostaglandin D synthase isoforms and proteins belonging to the complement system as correlated to neuroinflammation; high concentration of serum urate which has been linked to a reduced risk of developing PD and been proposed for use in neuroprotective trials to verify

disease progression; and the recently proposed skin biopsy test for small periphery fibers reduction detection. Finally, on the basis of a growing belief that iron levels in the brain might correlate to degree of vulnerability to PD, transcranial sonography showing hyperechogenicity is used as a marker of susceptibility. None of these tests however, has reached the phase of clinical screening, underlining the necessity of studies aimed at finding early predictors of the disease.

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NCI BIOMARKER INITIATIVES: PHYSICAL STANDARDS FOR IMAGING AND PROTEOMICS

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Advancing imaging research to serve as a critical element in multi-centre biomarker clinical trials necessitates that methodologies need to be developed, optimised and validated using commercial imaging platforms. This applies particularly to quantitative imaging as a biomarker for the prediction and measurement of response to drug or other forms of therapy including image-guided interventions (*i.e.*, especially in view of the emerging era of personalised medicine and therapy strategies). There is a critical need for common infrastructures and resources that can support quantitative imaging and quality assurance methods and a common means for their physical validation. Some examples of current resources are listed below.
National Cancer Institute (NCI):ACRIN:
http:// imaging.cancer.gov/clinicaltrials/acrin/
NCI: Quantitative Imaging for Evaluation of Responses to Cancer Therapies (U01)
http://grants.nih.gov/grants/guide/pa-files/PAR-08-225.html
NCI LIDC and RIDER Reference Image Databases:
http://imaging.cancer.gov/reportsandpublications/ReportsandPresentations/LungImaging
FDA Critical Path Initiative:
http://www.fda.gov/oc/ initiatives/criticalpath/initiative.html
NCI Proteomics Initiative: http://proteomics.cancer.gov/
FNIH NCI Biomarker Consortium:
http://www.biomarkersconsortium
NIST Interagency Workshop on Biomarkers:
http://usms.nist.gov/workshops/bioimaging.htm

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MASS SPECTROMETRY METHODS FOR THE FAST SCREENING OF BIOMARKER CANDIDATES

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There is a growing interest in developing absolute quantification methods for proteins in clinical samples by mass spectrometry. Nowadays, many candidate biomarkers are discovered using mass spectrometry. When antibodies are available, the validity of the candidate biomarker may be tested by an immunoassay methodology. For those candidates where antibodies are not available, a targeted mass spectrometric approach could be designed and applied successfully. Another important feature of a mass spectrometer is its capacity to quantify a number of different compounds in a single run. This is important because there is a growing awareness that for reliable disease diagnosis more than one biomarker is needed.

The selected reaction monitoring (SRM) technique is an alternative to the immunoassay method for protein quantification. A triple quadrupole (QqQ) mass analyser is optimally designed to measure candidate biomarkers in complex biological samples. The MALDI-QqQ mass spectrometer offers the following features: excellent sensitivity (femtomole level); reproducibilities of better than 15% ; a linear dynamic range of 3 to 4 orders of magnitude; rapid quantification of peptides and drugs in biological samples; simple sample preparation procedures that can be performed off-line and the ability to store samples on MALDI target plates for analysis at any convenient time.

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THE CONTRIBUTIVE ROLE OF LABORATORY MEDICINE TO PREVENTION

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Laboratory medicine is involved in more than seventy percent of medical decisions. The evolution of laboratory medicine is constant and an important driver for such evolution is the assimilation of new technologies. Genomics, pharmacogenomics and proteomics are now part of the core competencies of laboratory professionals, in addition to the existing arsenal of circulating biomarkers. Genomic and pharmacogenomic approaches are interesting for their potential to determine genetic susceptibilities to different disorders, both on individual and population scales, and to estimate the individual genetic sensibility to drugs, to optimise drug therapy, to prevent major adverse effects and, in the end they will guide physicians toward more appropriate treatments.

Nowadays, a compelling evidence-base exists for the use of genomic tools and targeted biomarkers in laboratories' daily practice to participate in the effort of individualising patient care and optimising healthcare expenses.

In conclusion, laboratory medicine, through the constant integration of new technologies, becomes an important player for the primary prevention of disorders and in the evaluation of responses to drugs.

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ETHICAL ASPECTS IN PREDICTIVE DIAGNOSIS, TARGETED PREVENTION AND PERSONALISED TREATMENT

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Trust and confidence should prevail when developing new research avenues and new testing capacities. Ethics provides a framework for analysing the issues, tensions, risks and benefits in the light of a certain corpus of values. It can be a governance tool, but it does not provide a tool kit of solutions that make tensions disappear! An important issue is first to avoid hype.

The essential elements of ethics are: transparency of information; clarification of the status of the tests and information provided; a clear definition of the clinical utility criteria, prior to marketing for health purposes; the highest privacy protection; strong regulation against the use of information not motivated by the utility for patients' health; the education of health professionals; the accompanying measures and adequate counselling of patients (families) as part of the service provided; the appropriate organisation to allow patients to get involved in governance structures; the provision of validated, independent and updated information on any test proposed.

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ETHICAL ISSUES IN PREDICTIVE MEDICINE

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The novel concept of predictive medicine has the potential to be generally accepted since correct and plausible predictions will bring a higher quality of life to the patient. His/her rights, however, should guarantee that the patient's data cannot be analysed and consequently, the prediction cannot be made, without either prior written consent or any other form of active approval that is manageable with current information technology.

If informed of a predictive diagnosis, the patient must always be told that the particular prediction is based upon the latest knowledge available and that this may be refined, or even changed, when new knowledge or data is available and entered into the system.

Legislatively and technically, the patient should be guaranteed permission to view his/her own medical records and to check who else has access to his/her medical records, changes made, if any, and who authorises access and for what purpose, as well as any other possible data logged.

The ethical aspect of predictive medicine, of course, must be supported by implementing relevant new legislation, which must be clear and effective enough to eliminate any possibility of misusing any component of the process. No discrimination on the basis of prediction must be allowed under the new legislation.

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COST – BENEFIT MODEL OF PREDICTIVE DIAGNOSIS, PREVENTION AND PERSONALISED TREATMENT

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To many health policy analysts it is an unquestioned assumption that in the face of limited healthcare resources, those resources should be allocated so as to maximise the health benefits they produce, measured by either the aggregate health status or disease burden of a population. To determine potential benefits some examples considering efficiency, effectiveness and socioeconomic assessment of predictive diagnosis and targeted prevention are here presented.

1. Predictive diagnosis and targeted prevention are key priorities for increasing government and policy maker stakeholders' capacity in planning health strategy and in implementing appropriate measures for an optimised and sustainable cost-benefit health policy.

2. The effectiveness of predictive diagnosis and targeted prevention considers the results in terms of the additional costs versus benefits per year of healthy life gained from the intervention.

3. Patients' family time and resources, professional activity and participation in the social dimension are relevant to determining whether an intervention creates overall positive cost-benefit impact.

4. Finally, the development in Europe of a health policy focusing on predictive diagnosis and targeted prevention could create jobs and could bring a positive impact to the health market stakeholders.

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TECHNOLOGY TRANSFER FROM ACADEMIA TO INDUSTRY: BARRIERS FOR MARKETING AND HOW TO OVERCOME THEM

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Universities are a rich source of identification of biomarkers. Yet only a few biomarkers have crossed the line to industry. The reasons are for example, a lack of generally applied standards of study design and data analysis, lack of funding and infrastructure for studies with sufficient statistical power and a lack of knowledge of what is requested by industry.

Key recommendations to address this problem include the following: it will be essential to standardise protocols for research on biomarkers providing a certain level of reliability for companies intending to pursue these projects. There is a need to foster interdisciplinary research projects between scientists producing data which are scientifically as well as clinically relevant. In addition, there is a need to extend funding systems to support proof of concept studies, including setting up translational research centres. Technology transfer is often hampered by a lack of basic knowledge of business-related issues by the scientist. Thus, it would be advantageous to intensify educating researchers on these subjects. It would be beneficial to establish "helpdesks" advising scientists and technology transfer managers on various topics regarding clinical development. It would be helpful to pursue the dissemination of appropriate templates for relevant types of legal contracts. Furthermore, the technology transfer landscape should be further developed.

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INFORMATION SYSTEMS AS AN ESSENTIAL COMPONENT OF PREDICTIVE, PREVENTIVE AND PERSONALIZED MEDICINE

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Current health care system and patients' data are not well organized and structured for the optimal outcome and benefit of the patient. Thus, patient's medical records are not interpreted in a complex manner. The clinical databases are not interconnected and there is a very low level of relevant data sharing, if any. Analysis of available clinical data and data pattern recognition emerge as important tools for early prediction, primarily based on even minor changes, which may later lead to major manifestation of symptoms of a particular disease. The role of complex, proper and accurate clinical information processing is therefore crucial.

The final aim of information systems in predictive, preventive and personalised medicine should be a complex interactive computer model, including human metabolic pathways and biological interactions, capable of predicting possible changes on the basis of knowledge acquired by worldwide computer data analysis and giving plausible predictions that will allow clinicians to avoid unexpected health problems.

Predictive medicine and personalised treatment should now use the advances of current information technology and get medicine to the level where patients do receive the best of what contemporary science and technology can offer.